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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/536,087	03/24/2000	Michael J. Detmar	10287-051001	2190

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 01/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/536,087	DETMAR ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2002 and 13 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7,13-23,53-61,63-68 and 75-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6, 7, 13-23, 53-61, 63-68, and 75-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Misook Yu.

DETAILED ACTION

Applicant's amendment, formal drawing, and Dr. Detmar's declaration filed on 10-7-2002 and supplemental response and Dr. Detmar's declaration filed on 11-13-2002 are acknowledged.

Claims 1, 6, 7, 13-23, 53-61, 63-68, and 75-87 are pending and examined on merits.

Claim Rejections - 35 USC § 103

Rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Panetti et el, in view of Volpert et al, Ferrara, Laherty et al, LaBell et al **is withdrawn** because applicant's argument is convincing.

NEW GROUNDS OF REJECTION and Rejections of Record Combined

Claim Rejections - 35 USC § 112

Enablement

Claims 1, 6, 7, 13-23, 53-61, 63-68, 75, 76, and 84-87 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to **enable** one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection has several aspects.

First, claims 1, 13-23, and 53-74 (now cancelled claims are also included here for clarification of what was rejected in the previous Office action) were rejected because the claims were reciting various sizes of SEQ ID NO:2 fragments and also reciting polypeptides at least 60-99 % homology to SEQ ID NO:2. Applicant argues that the newly amended claims 1, 6, 7, 13-23, 53-61, 63-68, 75, 76, and 84-87 now recite a TSP-2 at least 90 % identical to SEQ ID NO:2 or a fragment thereof having endothelical cell migration inhibition activity and also argues that it is a routine procedure in the art to make any size fragment or change any amino acid in a known protein such as TSP-2.

Making various fragments or mutations in a known protein is a routine molecular biology technique but the Office maintains that undue experimentation is required to make a fragment that retains the function cited in the instant claims because the specification does not teach the specific structures responsible for inhibiting endothelical cell migration activity in light of the art recognized unpredictability in protein chemistry. Note Paragraph # 6 of the previous Office action (Paper No. 10).

Second, claims 1, 6, 7, 13-23, 53-61, 63-68, 75, 76, and 84-87 are not enabled because the specification does not teach a method of treating a disorder using the active steps of the instant claims. The active step of the instant invention is to administer a TSP-2 protein or its fragments. Dr. Detmar's declaration states that the instant invention is enabled because Figure 3A and 3B show in vivo demonstration of skin cancer treatment, and applicant argues that the specification describes in vivo skin cancer treatment by TSP-2 at Figures 3A and 3B. However, the in vivo demonstration does not use the instant active step but uses a different method (i.e., administering DNA, not protein). Therefore, applicant argument and Dr. Detmar's declaration is not commensurate in scope with the invention. As for the in vivo data demonstrated in Fig. 3 attached with Dr. Detmar's declaration filed on 11-13-2002, it is not clear if the mice was give DNA or purified protein and further it is new matter because the specification as originally filed did not describe that the specific protein fragment; note the new matter rejection below. Therefore, the data will be excluded in the enablement analysis of instant method. The specification does not disclose any in vivo disorder treatment using the active step of instant invention. The guidance and the example in the specification is administering a nucleic acid molecule and there is no example or guidance about administering a protein. Gene therapy is different from administering a protein because gene therapy does not have to worry about proteases and protein degradation but protein therapy have to consider these factors. Administering a protein into the right target also pose a different problem than gene therapy. A peptide or protein must accomplish several tasks to be effective *in vivo*. It must be delivered into the target cells and interact at the proper site of action. Also protein and peptide concentration must be at a sufficient concentration and for a sufficient period of time. The proteins may be

inactivated in vivo before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of a peptide or protein. Peptide or polypeptide degradation is a problem well known in the art, in view of the presence of different proteases in vivo. US PAT 4,925,677 teaches that a protein, albumin is degradable by proteolytic enzymes (column 4 lines 4-18). Kastin, AJ, 2001, Life Science, 69(11): 1305-12, teach at the abstract and paragraph bridging page 1310 and 1311 that peptides are degraded at different regions in rat cerebral microvessels. Frost, SJ, 1993, J Cell Biochem, 52(2): 227-36 teach that peptides are degraded by cell-surface peptidase activity on endothelial cells (see the abstract).

The specification does not teach any in vivo treatment method of any disease in the instant claims using the product in commensurate in scope of the invention. The art recognizes that method of treating cancer or any of the specific diseases listed in the instant claims are is not trivial matter. It is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para of column 1). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptides or protein would be useful for treating cancer or any other diseases listed in the instant claims. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a

number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, one skilled in the art would accept without doubt the assertion that the claimed peptides or proteins would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2). Further, Bellone et al (2000, J. Immunology, vol. 165, pages 2651-2656) teach that in vivo therapy using a peptide or DNA encoding the same peptide does not lead to same result and unpredictable, therefore experimental data is necessary to validate efficacy of a therapeutic; See Table 1 at page 2654.

Art recognizes cancer treatment is not a trivial matter. The specification provides insufficient guidance with regard to these issues and provides no working examples which would allow one of skill in the art to practice the invention without undue experimentation.

Written Description

Claims 1, 6, 7, 13-23, 53-61, 63-68, 75, 76, and 84-87 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed

invention. Applicant argues that the instant claims have been narrowed to fragments of TSP-2 with endothelical cell proliferation inhibiting activity and also narrowed to at least 90 % to 99 % identical to SEQ ID NO:2. However, the Office maintains this rejection because the instant claims still lacks written description of at least 90 % to 99 % identical to SEQ ID NO:2 and also lacks written description of a TSP-2 or its fragments capable of accomplishing the purpose stated in the preamble of the instant claims.

New matter

The new claims 77-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed invention. The claims are interpreted as drawn to method of treating a disorder using the an amino acid sequence encoded by the three specific nucleotide sequences listed in the instant claims. This examiner is unable to find the support for the claims in the originally disclosed specification. Applicant is requested to point out the support for the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
January 26, 2003

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